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The contribution of infant formula to the food survey-based dietary exposure of nine selected elements

Tobias Höpfner[1], Melanie Wollenberg[1], Anna Jäger[1], Mandy Stadion[1], Christian Jung[1], Anna-Lena Klook[2], Oliver Lindtner[1]

[1]Department of Exposure, German Federal Institute for Risk Assessment (BfR), Berlin 10589, Germany.
[2]Institute of Agricultural and Nutritional Sciences, Martin-Luther-University Halle-Wittenberg, Halle 06108, Germany.

Correspondence to: Tobias Höpfner, Department of Exposure, German Federal Institute for Risk Assessment (BfR), Max-Dohrn-Straße 8-10, Berlin 10589, Germany. E-mail: tobias.hoepfner@bfr.bund.de

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Abstract

Infants and toddlers are exposed to environmental contaminants and elements also via food. Due to its high proportion in young children's diet, infant formula can contribute significantly to exposure. The present study describes the exposure to contaminants and elements such as inorganic arsenic (iAs), cadmium (Cd), chromium (Cr), manganese (Mn), mercury (Hg), nickel (Ni), lead (Pb), selenium (Se), and zinc (Zn) via formula consumption and classifies total dietary exposure in children aged 0.5-3 years in Germany. The assessment of long-term dietary exposure was based on data from the first total diet study (TDS) in Germany, the BfR MEAL Study, and the nutrition survey KiESEL. Results were compared to existing health-based guidance values (HBGV) or the margin of exposure (MoE) approach was used. The exposure of Cr, Ni, and Se was well below the corresponding HBGV. No HBGV was established for Hg, so the results were transformed into inorganic Hg. The Mn and Zn exposures were close to the HBGV in the 95th percentile and the MoE for Pb exposure was close to one. The MoE for iAs was below one for all children, and Cd levels exceeded the HBGV for about 30% of infants and toddlers. These results can support risk managers in continuing and prioritizing reduction strategies to reduce the levels of contaminants in food. Exposure to contaminants, particularly Mn, Zn, Pb, iAs, and Cd, through formula consumption should be further monitored.

Keywords: Total diet study, dietary exposure, risk assessment, infant formula, contaminants, elements

INTRODUCTION

The National Breastfeeding Commission in Germany recommends exclusive breastfeeding up to 4 or 6 months of age[1]. From the 5th to 7th month of life, breast milk is deemed no longer sufficient to meet energy requirements and complementary foods should be introduced. Even though breast milk is the gold standard in terms of nutrients and other health benefits[2], in some cases, infants may need to be fed infant formula instead of breast milk. Depending on the age of the infant, either infant formula or follow-on formula can be part of the diet. Infant formula (pre- and 1) and follow-on formula (2 and 3) differ in terms of their nutrient composition. Although there are national strategies to promote breastfeeding[1], studies from Germany show that the proportion of infants who are fed exclusively with breast milk is decreasing and infants who receive infant formula in addition or exclusively are increasing[3,4].

The safety and quality of infant formula is an important concern for both parents and health authorities. Many contaminants, such as heavy metals, occur naturally in the rocks of the earth's crust or in groundwater. They enter the environment via various routes (e.g., car traffic, pesticides), can contaminate food[5], and some subsequently accumulate in the body, potentially inducing health effects[6-8]. A major environmental contaminants exposure pathway for infants and toddlers is via diet. Infants and young children are particularly vulnerable to contaminants due to their high total quantity of food consumed with respect to body weight and the reduced number of food categories eaten[9]. The minimum and maximum content of nutrients in infant formula is set by EFSA and must be adhered to by the manufacturers[10,11]. The Codex Alimentarius specifies maximum levels of contaminants in infant formula, but Codex standards are not mandatory in a legal sense for manufacturers[12]. Legal binding maximum levels for contaminants and toxins in infant formula are set by the European Commission[13].

Environmental contaminants have been measured in infant formula in the US, Brazil, New Zealand, and Europe[14-17]. Infants fed exclusively with infant formula are 8 times more exposed to environmental contaminants than those who are not[18]. In Germany, contaminants in infant formula have so far been analyzed in the national food monitoring. A risk assessment for cadmium (Cd) and lead (Pb) was carried out by the German Federal Institute for Risk Assessment (BfR) in 2018, with consumption data from the nutrition survey VELS[19]. Results have shown that health impairments through Cd are not likely for infants with an average and high consumption of "dairy food in powder form" and "ready-to-eat" infant formula. Additionally, Pb uptake was below the $BMDL_{01}$ (benchmark dose lower confidence limit) value for developmental neurotoxicity possibly caused by Pb[20]. With the BfR Meal Study, which is the first total diet study (TDS) in Germany, current occurrence data from infant and follow-on formula on contaminants are available[21,22]. Furthermore, the KiESEL study provides current consumption data from Germany for children's nutrition[23].

While dietary exposure assessments for the total child population in Germany are already available for Cd[21], arsenic species[24], and methylmercury[25], the present publication focuses on dietary exposure to environmental contaminants specifically in infants and toddlers consuming formula. The exposure from infant formula is only related to the overall exposure in infants consuming formula alongside other foods. This publication focuses on inorganic arsenic (iAs), cadmium (Cd), chromium (Cr), manganese (Mn), inorganic mercury (Hg), nickel (Ni), lead (Pb), selenium (Se), and zinc (Zn).

EXPERIMENTAL

Consumption data

Consumption data of the KiESEL study ("Children's Nutrition Survey to Record Food Consumption") for children aged 0.5 to < 6 years were used to estimate dietary exposure. The KiESEL study was a crosssectional representative nutrition survey conducted at the BfR between 2014 and 2017. KiESEL included 1,008 children from all over Germany whose families completed weighing dietary records (additionally, estimation records were provided by childcare facilities) on three consecutive days plus one non-consecutive day[23].

The KiESEL study included a total of 114 children who consumed at least partially infant formula, but were not breastfed. For this publication, consumption data from children aged 0.5 to < 1 year (infants) (n = 51) and 1 to < 3 years (toddlers) (n = 63) were considered. Breastfed children (n = 13) were excluded from the analysis, since no data on the amount of breast milk consumed were collected.

Intake was counted if infant formula was consumed as the sole meal or in addition to the main meal (in combination with other foods) on at least one of the four protocol days or if infant formula was used to prepare meals (e.g., porridge).

Occurrence data

The exposure assessment was based on the occurrence data from the BfR MEAL Study ("Meals for exposure assessment and analysis of foods"). The BfR Meal Study was commissioned by the German Federal Ministry of Food and Agriculture in 2015 and is the first German TDS. It covers more than 90% of the food consumed by the German population in the age groups of 0.5 to < 5 years and 14 to > 65 years[22]. A total of 356 foods were sampled and analyzed for more than 300 individual substances. These included iAs, Cd, Cr, Mn, Hg, Ni, Pb, Se, and Zn, which are discussed in this publication. The substances were selected according to previous exposure assessments that indicated potential issues for children[9,15,26,27] and/or infant formula[28].

The food pools of the BfR MEAL Study were collected according to expected variations in regionality (north, east, south, west), seasonality (import and national production; or stable and pasture season; or purchasing at two different times of the year), and type of production (organic or conventional production) between 2017 and 2019. Foods with no expected variation in the previous criteria were sampled throughout the year in the area of Berlin and could include both organically and conventionally produced food items. According to this sampling structure, 869 food pools were created for analysis of As, Cd, Cr, Hg, Mn, Ni, Pb, Se, and Zn[29], with one to ten pools for each food item. For iAs, only a selection of 52 foods was analyzed, where iAs could be expected.

One of the 356 foods was "infant formula", with a single pool that combined 15 subsamples of different products. The "infant formula" pool contained eight infant formula subsamples (pre and 1), four follow-on formula subsamples (2 and 3), two hypoallergenic infant formula subsamples, and one subsample of infant formula for special medical needs (anti-reflux and diarrhea) based on cow milk. The products were mixed and homogenized. Since the preparation of infant formula often differs from the manufacturer's instructions, the formulae were analyzed in their powdered form. The contaminant concentration in drinking water, as used for exposure assessment, was based on four pools originating from the MEAL study kitchen. Drinking water was also sampled regionally (n = 29 pools). Regionally sampled drinking water pools were excluded from the analysis since water from the MEAL kitchen was used for all food preparations.

All food pools were analyzed in duplicate. To ensure quality and consistency of the analytical measurements, 5% to 10% of pools of all foods were sent to the laboratory under a different pool number and compared to the initial measurements.

Further details on the data collection, preparation, and homogenization are described elsewhere[21,22].

Exposure was assessed on the basis of food pools containing only foods produced conventionally.

Analysis of As, iAs, Cd, Cr, Ni, Mn, Pb, Se, and Zn in food pools

The determination of the elements As, Cd, Cr, Ni, Mn, Pb, Se, and Zn in food pools of the BfR MEAL Study was conducted by inductively coupled plasma mass spectrometry (ICP-MS) at an external accredited contract laboratory. Microwave digestion followed DIN EN 13805:2014. In short, 0.4-0.7 g of solid or 2.0 g of liquid food homogenates were treated with 4 mL HNO_3 (65% v/v) and 2 mL H_2O_2 (Merck KGaA, Darmstadt, Germany) in sealed vessels and heated up to 210 °C for 25 min using a MARS 6 microwave digestion system (CEM, Kamp-Linfort, Germany). After cooling down to room temperature, digested samples were dissolved in 5 mL HNO_3 (65% v/v) and diluted to a volume of 25 mL by adding purified water (Sartorius Lab Instruments, Göttingen, Germany).

Levels of investigated elements were determined by ICP-MS by iCAP Q/X-Series 2 systems (Thermo Fischer Scientific, Bremen, Germany) or a 7800 ICP-MS system (Agilent Technologies, Waldbronn, Germany). Each sample was analyzed in duplicate. For quality control, laboratory blank solutions were included in every run, as well as a reference material (NIST 1849; milk powder). Levels were quantified via external 8-point calibration.

Detailed information on instrumental conditions and used internal standards (Merck KGaA) are listed in Supplementary Table 1. Individual limits of detection (LOD) and limits of quantification (LOQ) for the different sample matrices, as well as the extended measurement uncertainties, are provided in Table 1.

The iAs content was determined for a limited number of foods that were known to contain high levels of iAs. The analysis was performed by the University of Potsdam and is described in detail elsewhere[30]. In short, 20 mL trifluoroacetic acid (0.02 M) with 6% (V/V) H_2O_2 was added to 1 g ± 0.1 mg of the sample. After sonification for 15 min at 35 °C, the solution was placed in a water bath for 60 min at 95 °C. Following further sonification, the extracts were centrifuged twice (15 min at 7,164 rcf and an aliquot of 2 mL for 15 min at 21,380 rcf). A 200 µL aliquot of the supernatant was used for analysis with anion exchange high-performance liquid chromatography (HPLC)-ICP-MS/MS. Concentrations of iAs were determined as As(V), since oxidation with H_2O_2 converted As(III) to As(V). The quantification was performed using external calibration against standards based on peak areas. Obtained LOD and LOQ for iAs were 0.001 and 0.003 mg/kg, respectively. For all other foods (including infant formula), conversion factors were applied to estimate the content of iAs from total As. The conversion factors considered 70% of the total arsenic as iAs, as suggested by EFSA[31].

Analysis of Hg in food pools and drinking water

Levels of total Hg in food pools of the BfR MEAL Study were examined by an external accredited contract laboratory via a direct Hg analyzer (DMA-80, Milestone Srl, Sorisole, Italy). For dry and moist food homogenates, the method was already described elsewhere[25]. Briefly, 200-400 mg of undiluted liquid and solid samples were placed in quartz and Ni alloy vessels, respectively. After an incineration step, the resulting Hg vapors were amalgamated with gold and Hg levels were determined at 253.7 nm.

For quality control, tomato leaves were measured in every tenth run as a certified reference material (NIST 1573a). Samples were analyzed in duplicate. LODs, LOQs, and the extended measurement uncertainty for the detection of Hg are listed in Table 1.

Table 1. LOD, LOQ and measurement uncertainty for the analysis of elements*

Parameter	LOD (mg/kg)			LOQ (mg/kg)			Expanded measurement uncertainty (%)
	Dry matrices	Moist matrices	Drinking water	Dry matrices	Moist matrices	Drinking water	
Arsenic	0.002	0.001	0.0007	0.01	0.002	0.002	30
iAs	0.001	0.001	0.001	0.003	0.003	0.003	-**
Cd	0.002	0.0003	0.00007	0.005	0.001	0.0002	20
Cr	0.02	0.003	0.002	0.05	0.01	0.005	10
Pb	0.001	0.001	0.00007	0.004	0.002	0.0002	20
Mn	0.008	0.002	0.0003	0.03	0.006	0.001	10
Hg	0.003	0.001	-**	0.005	0.002	0.0001	30
Ni	0.03	0.006	0.0003	0.1	0.02	0.001	20
Se	0.003	0.003	0.003	0.01	0.01	0.01	10
Zn	0.03	0.006	0.0003	0.1	0.02	0.001	10

*Different LODs and LOQs apply to foods with different matrices; the LOQ and LOD for dry matrices was applied for the analysis of infant formula. **Not specified. LOD: Limit of detection; LOQ: limit of quantification; iAs: inorganic arsenic; Cd: cadmium; Cr: chromium; Pb: lead; Mn: manganese; Hg: mercury; Ni: nickel; Se: selenium; Zn: zinc.

The analysis of total Hg in drinking water was carried out via cold vapor atomic absorption spectrometry according to DIN EN ISO 12846 as described elsewhere[32]. In brief, 100 mL per sample was incubated with 2 mL of a KBr-$KBrO_3$ solution (Merck KGaA) for 30 min at room temperature. Subsequently, 100 µL of an NH_4Cl solution (Merck KGaA) was added to 10 mL of each sample. Hg levels were analyzed using a Hydra II AA system (Teledyne Leeman Labs, Mason, Ohio, USA). An acidic stannous chloride solution (0.53 mol/L) was used to receive elemental Hg. Hg levels were analyzed at 253.7 nm.

The quantification of total Hg in food and drinking water samples was realized by external 5-point calibration with standardized Hg solutions.

Exposure calculation

In the BfR MEAL Study, foods were analyzed "as consumed". This analysis on similar food aggregation levels enables nearly direct matching to the consumed foods reported in the KiESEL study. Only few foods needed adaptation by conversion factors or application of standard recipes. For detailed information on the applied matching strategy, please refer to Kolbaum *et al.*[22]. Dietary exposure was assessed following a deterministic approach. To calculate long-term exposure (E), the mean concentrations (L) of a contaminant (j) in the individual MEAL foods (k) were multiplied by the daily average consumption (C) of the respective food (k) each child (i) reported and divided by the child's individual bodyweight (bw). Subsequently, exposure via single foods (total number: *n*) was summed up to estimate total long-term exposure for each child according to Equation (1)[33]. The calculation considered the upper bound (concentrations below the LOD were set to the value reported as the LOD; concentrations below the LOQ and above the LOD were replaced by the value reported as the LOQ) approach.

$$E_{i,j} = \sum_{k=1}^{n} \frac{C_{i,k} * L_{k,j}}{bw_i} \quad (1)$$

Results for total exposure were compared to respective reference values of each substance obtained from literature. In addition to total exposure estimations, the analysis of the present study included the calculation of each child's individual consumption of infant formula and respective exposure thereof, as well as the contribution of the exposure via infant formula to total exposure of a substance for each individual child. For each parameter, the mean, median, and 95th percentiles among the group of children considered were reported. The statistical analyses were done by using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the packages "base", "tidyr", "openxlsx", "tables", "Hmisc", "here" and "data.table", as well as Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

RESULTS AND DISCUSSION

Occurrence data

The upper bound mean concentrations are presented in Table 2 for powdered infant formula and in Table 3 for drinking water. Since the TDS approach is not appropriate for covering the variability of occurrence data across individual products, data obtained by the BfR MEAL Study were compared to published results from the German national monitoring [Table 2][34,35]. In addition to the mean values, the minimum and maximum values from the food monitoring were also reported in Table 2.

Generally, mean concentrations in the BfR MEAL Study were lower compared to the monitoring concentrations, which is mostly a result of higher detection and quantification limits in food monitoring. In contrast, lower limits have been reported for Hg analysis in monitoring, resulting in higher mean Hg concentration in the BfR MEAL Study. However, Hg concentrations in infant formula in both sampling campaigns were below the LOQ. This is congruent with the results of the first French TDS[36].

Results of the German food monitoring from the analysis on iAs were also 100% below the LOQ. The concentration of iAs determined in the BfR MEAL Study (4.55 µg/kg) was well below the LOQ of the German food monitoring. Similar low levels have been reported across Europe[37] and the US[14].

The European Union has set a maximum level of 0.01 mg/kg (equivalent to 10 µg/kg) for Cd in "food in powder form, based on cow's milk"[20]. The Cd content estimated in the BfR Meal Study was 4.00 µg/kg, which is well below the specified limit. This is in the same range as the monitoring data (mean 5.94 µg/kg). Similar occurrence data for infant and follow-on formulae were found in international studies[38-42].

Considerable variations in the level of Cr and Ni in infant formula have been reported across Europe, with an average content exceeding the Cr and Ni content determined in the present study[43,44]. Fluctuations in the content of contaminants in infant formula are already well-known from Cr, which may be due to inadequate control of contamination in the sample handling[43].

The Pb concentration estimated in the German food monitoring was twice as high as the Pb content determined in the BfR MEAL Study. Although distinct variations for Pb content in infant formula are known from other studies[26], the higher values in the food monitoring are most likely due to comparatively high LOQs and a high proportion below LOQ.

The Mn and Se content were also in the same order of magnitude as occurrence data from Italy[38] and Brazil[17]. However, much lower data on Zn content were reported from Brazil. Results from the German food monitoring revealed a strong variability in the levels of the three substances. Such variability is also described in literature[16,17] and is attributed to the manufacturing process of infant and follow-on formula. Mn, Se, and Zn are essential elements and are already used in the production of infant formula or added to the product[45,46].

For the preparation of infant formula, the dry powder is usually mixed with drinking water. Therefore, Table 3 also summarizes the analytical results of drinking water in the BfR MEAL Study.

Table 2. Occurrence data of iAs, Cd, Cr, Pb, Mn, Hg, Ni, Se and Zn in powdered infant formula measured in the BfR MEAL Study as used for exposure assessment and data of powdered infant formula measured in the German food monitoring for comparison

Substance	Infant formula				
	BfR MEAL study		German food monitoring		
	Mean*	Measurements < LOQ [%]**	*n*	Mean (Min.-Max.)	Samples < LOQ [%]***
Results in μg/kg					
iAs	4.55	50	3	20.0 (20.0-20.0)	100
Cd	4.00	50	93	5.94 (1.00-17.0)	51
Cr	32.8	0	75	78.5 (3.50-200)	80
Pb	4.00	75	77	9.99 (1.00-20.0)	91
Mn	840	0	74	1,182 (50.0-3,533)	18
Hg	3.00	100	19	1.57 (1.00-3.14)	100
Ni	78.8	50	70	156 (8.00-600)	87
Se	130	0	77	211 (11.8-420)	4
Results in mg/kg					
Zn	40.0	0	76	35.4 (0.30-55.7)	0

*Only mean is presented because analysis of substance content is based on multiple determinations of one pooled sample. **Proportion below LOQ is based on one measurement for Hg and four measurements for all other substances. ***iAs: LOD 20 μg/kg, LOQ 60 μg/kg; Cd: LOD 0.3-5 μg/kg, LOQ 1-17 μg/kg; Cr: LOD 1-75 μg/kg, LOQ 3.5-150 μg/kg; Pb: LOD 0.3-20 μg/kg, LOQ 1-40 μg/kg; Mn: LOD 1.6-750 μg/kg, LOQ 5.5-1,500 μg/kg; Hg: LOD 0.45-3.1 μg/kg, LOQ 1.5-10.6 μg/kg; Ni: LOD 2.4-600 μg/kg, LOQ 8-1,200 μg/kg; Se: LOD 2-100 μg/kg, LOQ 6-200 μg/kg; Zn: LOD 0.02-3 mg/kg, LOQ 0.07-6 mg/kg. iAs: Inorganic arsenic; Cd: cadmium; Cr: chromium; Pb: lead; Mn: manganese; Hg: mercury; Ni: nickel; Se: selenium; Zn: zinc; LOQ: limit of quantification; *n*: number of samples; Min.: minimum; Max.: maximum; LOD: limit of detection.

Table 3. Occurrence data from the BfR MEAL Study for iAs, Cd, Cr, Pb, Mn, Hg, Ni, Se and Zn in drinking water (as used for exposure assessment) and regionally sampled drinking water for comparison in μg/kg

Substance	Drinking water used for preparations in the BfR MEAL Study			Regionally sampled drinking water of the BfR MEAL Study	
	Mean	Min.-Max.*	Pools < LOQ [%]	Min.-Max.**	Pools < LOQ [%]
iAs	0.49		100	0.49-1.40	100
Cd	0.10	0.07-0.14	100	0.07-0.20	100
Cr	2.00		100	2.00-5.00	100
Pb	0.91	0.20-1.70	25	0.07-2.00	57
Mn	1.75	1.50-2.00	0	0.30-3.00	79
Hg	0.07		100	0.10***	100
Ni	2.50	1.00-4.50	50	0.30-5.00	79
Se	0.30		100	0.30-1.00	100
Zn	300	10.5-723	0	1.30-240	0

*Minimum and maximum are only given for varying occurrence data and were based on four pooled samples. **Minimum and maximum were based on 29 pooled samples. ***No LOD applied; all results below LOQ; concentration data were exclusively based on the value of the LOQ (upper bound approach). iAs: Inorganic arsenic; Cd: cadmium; Cr: chromium; Pb: lead; Mn: manganese; Hg: mercury; Ni: nickel; Se: selenium; Zn: zinc; Min.: minimum; Max.: maximum; LOQ: limit of quantification; LOD: limit of detection.

Consumption data

Among all the children considered, no child consumed exclusively infant formula. Bodyweight-related daily consumption of infant formula was generally higher in infants (median: 6.61 g/kg bw/day) than in toddlers (median: 3.86 g/kg bw/day) [Table 4]. In previous studies assessing exposure from infant formula, intake estimations were often used instead of recorded consumption data. Lin *et al.*, for example, estimated the intake from product sample instructions[47]. Children of 7-12 months were estimated to be fed 105 g/day and children of 13-24 months 100 g/day. Su *et al.* used amounts of infant formula recommended by the Chinese

Table 4. Consumption of Infant formula (dry weight) recorded in the KiESEL study among infants (< 1 year) and toddlers (1 to < 3 years), who consumed infant formula (breastfed children were excluded)

Age group	*n*	Children considered [%]	Consumption					
			g/kg bw/day			g/day		
			Mean	P50	P95	Mean	P50	P95
Infants (< 1 year)	51	89	8.01	6.61	15.8	69.4	54.3	142.7
Toddlers (1 to < 3 years)	63	20	4.46	3.86	8.38	48.9	39.6	83.3

n: Number of children [weighted for age, gender, region, regional structure (size of a community) and the education of the parents to ensure representativeness for the German population][23]; P50: 50th percentile; P95: 95th percentile.

Nutrition Society[41]. Verkaik-Kloosterman *et al.* reported a median habitual intake of formula of 592 mL/day for 7-month-old children, decreasing to 424 mL/day for 12-month-old children[48]. The actual amount of infant formula consumed was usually lower than the recommendations, as meals prepared according to the recommendations were not consumed in full and additional food was provided.

Exposure estimations

Results of long-term dietary exposure assessment are presented in Tables 5-7.

Differences in exposure between infants and toddlers were predominantly small [Table 5]. Compared to infants, toddlers were slightly more exposed to Mn, Ni, Se, and Zn, while infants showed slightly higher exposure to Cr and Pb. Table 5 shows that the proportion of infant formula in exposure was up to 64% (50th percentile) for infants and decreased with increasing age to a maximum of 43% (50th percentile) for toddlers.

The comparison of the calculated exposures to the health-based guidance values (HBGVs) is presented in Table 6.

Cr

Assuming that 100% of the total Cr corresponds to Cr(III), dietary Cr exposure in infants and toddlers was a maximum of 1% (95th percentile: 1.93-2.71 µg/kg bw/day) of the tolerable daily intake (TDI; 300 µg/kg bw/day) derived in 2014 by EFSA[43]. TDS-based exposure estimates from France[15] and England[55] were of a similar order of magnitude. A considerably higher exposure was calculated for older children (4-9 years) from Spain (29.4 µg/kg bw/day). Nevertheless, there was a low probability of exceeding the HBGV for excessive Cr intake[56].

Inorganic Hg

Since no HBGV was established on the total form of Hg and methylmercury was not expected in infant formula, the HBGV for inorganic Hg as derived by EFSA[51] was compared to the exposure estimates derived for inorganic Hg based on measurements of total Hg. In line with this EFSA approach, conversion factors were applied to estimate the content of inorganic Hg from total Hg. These conversion factors considered 20% of total Hg in fish and fish-based products as inorganic Hg. For molluscs and crustaceans, 50% of total Hg has been considered inorganic Hg. For other foods, all Hg was regarded as inorganic Hg[51]. Median exposure for inorganic Hg was estimated at 0.11 µg/kg bw/day for infants and toddlers [Table 5] and was well below the tolerable weekly intake [TWI; 4 µg/kg bw/week (0.57 µg/kg bw/day)]. No child exceeded the TWI. Consumption of infant formula accounted for 18% (0.02 µg/kg bw/day) of inorganic Hg exposure in infants and 8% (0.01 µg/kg bw/day) in toddlers. The estimated dietary exposure to inorganic Hg was in the same order of magnitude as results from France[15] and at the European level[51]. Consequently, EFSA stated

Table 5. Long-term dietary exposure of children consuming infant formula and contribution of infant formula to total exposure

Substance	Age group (years)	Exposure					
		Infant formula (proportion of total exposure in %)			Total*		
		Mean	P50	P95	Mean	P50	P95
Results in μg/kg bw/day							
iAs	0.5 to < 1	0.04 (18)	0.03	0.07	0.22	0.22	0.33
	1 to < 3	0.02 (10)	0.02	0.04	0.21	0.21	0.35
Cd	0.5 to < 1	0.03 (10)	0.03	0.06	0.30	0.32	0.48
	1 to < 3	0.02 (6)	0.02	0.03	0.32	0.30	0.64
Cr	0.5 to < 1	0.26 (19)	0.22	0.52	1.37	1.37	1.93
	1 to < 3	0.15 (8)	0.13	0.27	1.80	1.68	2.71
Pb	0.5 to < 1	0.03 (12)	0.03	0.06	0.25	0.26	0.33
	1 to < 3	0.02 (9)	0.02	0.03	0.23	0.22	0.39
Inorganic Hg	0.5 to < 1	0.02 (18)	0.02	0.05	0.11	0.11	0.18
	1 to < 3	0.01 (8)	0.01	0.03	0.12	0.11	0.21
Ni	0.5 to < 1	0.63 (20)	0.52	1.24	3.11	2.96	5.30
	1 to < 3	0.35 (9)	0.30	0.66	3.83	3.54	8.64
Results in μg/day							
Mn	0.5 to < 1	58.3 (7)	45.7	120	828	834	1,514
	1 to < 3	41.1 (4)	33.2	69.9	1,167	1,073	2,348
Se	0.5 to < 1	9.02 (53)	7.07	18.6	17.1	15.7	27.9
	1 to < 3	6.36 (31)	5.14	10.8	20.5	18.9	29.2
Zn	0.5 to < 1	2,778 (64)	2,175	5,711	4,310	4,087	7,601
	1 to < 3	1,957 (43)	1,584	3,333	4,539	4,700	6,542

Occurrence data were set to the upper bound scenario. *Total exposure is based on the individual total consumption of the KiESEL study participants and occurrence data for the 356 MEAL foods. P50: 50th percentile; P95: 95th percentile; bw: body weight; iAs: inorganic arsenic; Cd: cadmium; Cr: chromium; Pb: lead; Hg: mercury; Ni: nickel; Mn: manganese; Se: selenium; Zn: zinc.

Table 6. Comparison of dietary exposure with HBGVs for children consuming infant formula

Substance	Age group (years)	HBGV	% of HBGV			Children exceeding HBGV
			Mean	P50	P95	*n* (%)
Cd	0.5 to < 1	TWI = 2.5 μg/kg bw/week (0.36 μg/kg bw/day)[42]	84	89	133	16 (31)
	1 to < 3		89	84	178	18 (29)
Cr	0.5 to < 1	TDI = 300 μg/kg bw/day[43,49]*	0	0	1	0 (0)
	1 to < 3		1	1	1	0 (0)
Mn	0.5 to < 1	SLI = 2 mg/day[50]	41	42	76	1 (2)
	1 to < 3	SLI = 4 mg/day[50]	29	27	59	0 (0)
Inorganic Hg	0.5 to < 1	TWI = 4 μg/kg bw/week (0.57 μg/kg bw/day)[51]	20	19	32	0 (0)
	1 to < 3		20	19	36	0 (0)
Ni	0.5 to < 1	TDI = 13 μg/kg bw/day[44]	24	23	41	0 (0)
	1 to < 3		29	27	66	0 (0)
Se	0.5 to < 1	UL = 55 μg/day[52]	31	29	51	0 (0)
	1 to < 3	UL = 70 μg/day[52]	29	27	42	0 (0)
Zn	0.5 to < 1	-**	-	-	-	-
	1 to < 3	UL = 7 mg/day[53]	65	67	93	2 (3)

*TDI refers to Cr(III). **No UL established for children under one year. HBGVs: Health-based guidance values; P50: 50th percentile; P95: 95th percentile; *n*: number of children exceeding the HBGV; Cd: cadmium; TWI: tolerable weekly intake; bw: body weight; Cr: chromium; TDI: tolerable daily intake; Mn: manganese; SLI: safe level of intake; Hg: mercury; Ni: nickel; Se: selenium; UL: tolerable upper intake level; Zn: zinc.

Table 7. MoEs calculated for exposure to Pb and iAs for children consuming infant formula

Substance	Age group (years)	BMDL	MoE			Children below MoE of 1
			Mean	**P50**	**P95**	***n* (%)**
iAs	0.5 to < 1	$BMDL_{05}$ = 0.06 µg/kg bw/day[37]*	0.27	0.28	0.18	51 (100)
	1 to < 3		0.28	0.29	0.17	63 (100)
Pb	0.5 to < 1	$BMDL_{01}$ = 0.5 µg/kg bw/day[54]**	2.02	1.92	1.52	0 (0)
	1 to < 3		2.15	2.27	1.30	0 (0)

*Benchmark intake for skin cancer. **Benchmark intake for developmental neurotoxicity. MoE: Margin of exposure; Pb: lead; iAs: inorganic arsenic; BMDL: benchmark dose lower confidence limit; P50: 50th percentile; P95: 95th percentile; *n*: number of children with MoE below 1; bw: body weight.

that the estimated dietary exposure to inorganic Hg in Europe does not raise a concern.

Dietary exposure to methylmercury was assessed previously for the German child population and ranged from 0.069 to 0.21 µg/kg bw/week[25] and was well below the corresponding TWI (1.3 µg/kg bw/week)[51].

Ni

Ni exposure was estimated at 2.96-3.54 µg/kg bw/day in the median [Table 5]. The TDI (13 µg/kg bw/day) was not exceeded in the present study [Table 6]. The dietary Ni exposure of infants and toddlers was around a quarter of the TDI in the median. The determined Ni exposure was of the same order of magnitude as the Ni exposure of Dutch[27], British[55], French[15], and Italian[57] children. The Ni exposure at the European level, as estimated by EFSA, was much higher. The median Ni exposure between countries was 6.14 µg/kg bw/day for infants and 10.1 µg/kg bw/day for toddlers (upper bound). High-consuming infants and toddlers reached a median Ni exposure in the upper bound between 12.8 and 17.9 µg/kg bw/day, respectively, and in some cases exceeded the TDI (13 µg/kg bw/day). EFSA concluded that a health risk could arise[44]. Based on the present results, EFSA's high exposure values could not be confirmed for consumers of infant formula.

Se

The tolerable upper intake level (UL) for Se (infants: 55 µg/day; toddlers: 70 µg/day) was derived from a randomized controlled study on humans with Alopecia as a critical endpoint[52]. The exposure for Se was estimated at almost 30% of the UL (15.7 µg/day) in the median and 51% of the UL (27.9 µg/day) in the 95th percentile for infants [Table 6]. EFSA reported a similar Se exposure for German infants (9.6-10.6 µg/day; female-male) and toddlers (17.0-18.2 µg/day; female-male)[52]. Significantly higher Se exposure was reported for British children. Nevertheless, Se intake was well below the corresponding HBGV[55].

Pb

Dietary Pb intake for infants and toddlers was measured at 0.26 and 0.22 µg/kg bw/day, respectively, with 95th percentile exposures at 0.33 µg/kg bw/day for infants and 0.39 µg/kg bw/day for toddlers [Table 5]. Estimated Pb intake levels were similar to those of British and French children. British children aged 1.5-4.5 years had average Pb exposures of 0.25 µg/kg bw/day, rising to 0.42 µg/kg bw/day at the 97.5th percentile (upper bound)[55]. French children aged 7 months to 3 years had mean upper bound Pb exposures between 0.196 and 0.209 µg/kg bw/day, with an exposure in the 90th percentile ranging from 0.295 to 0.314 µg/kg bw/day[15]. The EFSA reported higher Pb exposures for European infants (1.09 µg/kg bw/day) and toddlers (1.54 µg/kg bw/day), with high-consuming infants and toddlers reaching 2.22 and 2.56 µg/kg bw/day[58]. Comparisons with previous EFSA findings showed average Pb intakes of 0.27 to 0.40 µg/kg bw/day for 3-month-olds consuming only infant formula, and 0.63 to 0.94 µg/kg bw/day for high-consumers[54]. In Turkey, Pb exposure from infant formula decreased with age, from 0.55 µg/kg bw/day for 7-12-month-olds to 0.07 μg/kg bw/day for 13-24-month-olds[39]. In Saudi Arabia, infants up to six months had Pb exposures of 0.21-0.50 μg/kg bw/day from infant formula, decreasing to 0.10-0.21 μg/kg bw/day for 7-12-month-olds, considering other infant foods as well. These estimates were based on product-specific consumption recommendations and average infant weights, which may differ from actual intakes[26]. EFSA derived a $BMDL_{01}$ for Pb intake of 0.50 μg/kg bw/day based on neurotoxic effects (IQ reduction)[54]. For infants and young children, the median margin of exposure (MoE) was approximately 2, with the lowest MoE of 1.30 observed in the 95th percentile of infants [Table 7]. Despite the low MoEs among high-consuming children, no participant had an MoE below one. Similar MoEs were observed in the French Infant-TDS[15]. However, EFSA's assessment indicates that the risk of neurotoxic effects cannot be ruled out for MoEs lower than 10.

Mn

Although it is known that excessive manganese intake can cause neurotoxicity, there is still insufficient data to establish a dose-response relationship and derive a UL. Instead, a safe level of intake was established[50]. The median exposure to Mn (infants: 0.83 mg/day; toddlers: 1,07 mg/day) was well below the safe level of intake of 2 and 4 mg/day [Table 5]. In contrast, Mn exposure was estimated at 76% of the safe level of intake for infants in the 95th percentile. Only one infant exceeded the safe level of intake [Table 6]. It must be noted that the safe level of intake cannot clearly define the proportion of people at risk because no intake level could be determined at which the risk of adverse effects increases. The Mn exposure for infants was of the same order of magnitude as the Mn exposure calculated by EFSA at the European level (0.59-1.51 mg/day). Toddlers had a lower exposure than the European average of the same age group (1.28-2.68 mg/day)[50]. Considerably higher Mn exposures were reported for British (168 μg/kg bw/day)[55] and Dutch (1,400 μg/kg bw/day)[27] children (bodyweight-related Mn exposure was estimated at 91 μg/kg bw/day for infants and 101 μg/kg bw/day for toddlers in the present study). In general, it must be noted that Mn may be added to supplements and foods. A reliable exposure assessment should consider both the intake of supplements and the consumption of fortified foods to minimize uncertainties.

Zn

The median Zn exposure (infants: 4.09 mg/day; toddlers: 4.70 mg/day) was comparable to the Zn exposure of British[55] and Dutch[27] children [Table 5]. Zn exposure of the same magnitude was also determined by EFSA for German toddlers[59]. In the Dutch study of 1- and 2-year-old children, follow-on formula was one of the three foods with the highest proportion of Zn exposure[27]. In the present study, infant formula contributed the most to Zn exposure at 64% (infants) and 43% (toddlers). The determined Zn exposure was compared with the UL established in 2002. The UL was derived for adults and adjusted for children by extrapolation. No UL has been established for infants under one year of age[53]. Dietary Zn exposure for toddlers was estimated at over 60% of the UL in the median and reached 93% of the UL in the 95th percentile, and only two toddlers exceeded the UL [Table 6].

iAs

The median dietary exposure to iAs was 0.22 μg/kg bw/day for infants and 0.21 μg/kg bw/day for toddlers [Table 5]. Dietary exposure was estimated for high-consuming children at 0.33 and 0.35 μg/kg bw/day. These results align with British and French studies, where dietary exposure amounted to 0.246 μg/kg bw/day for mean-consuming and 0.402 μg/kg bw/day for high-consuming British children[55]. Similar results were presented for French children between 1 and < 3 years. Toddlers in this age group showed a mean exposure for iAs in the amount of 0.221 μg/kg bw/day. Nevertheless, upper bound dietary exposure to iAs was with 0.387 μg/kg bw/day higher for French infants between 0.5 and < 1 year, especially for high-consuming infants (0.839 μg/kg bw/day)[15]. Dietary exposure to iAs in French children was based on occurrence data derived from conversion factors. In New Zealand, samples with detected total arsenic > 0.02 mg/kg were analyzed for iAs and conversion factors were applied for all other foods, considering 100% of total arsenic as iAs. Due to high conversion factors, the derived estimate could be interpreted as a worst-case scenario[31]. The resulting upper bound exposure for infants (0.79 µg/kg bw/day) from New Zealand clearly exceeded the intake of iAs of German infants[60]. EFSA's recently updated risk assessment estimated median exposures in Europe between 0.15-0.42 µg/kg bw/day for infants and 0.17-0.44 µg/kg bw/day (lower bound - upper bound) for toddlers. The contribution of "Infant formula and follow-on formula" varied strongly between lower bound (0%-4%) and upper bound (up to 63%) across European countries. For German infants, the contribution was 8%, and for toddlers, it was 2%, slightly below the results of the present study[61]. It must be taken into account that the present exposure assessment considers 70% of total arsenic to be iAs. However, studies on arsenic speciation in infant formula suggest that iAs is the predominant form of arsenic in infant formula[14]. This would lead to an underestimation of exposure. EFSA established a $BMDL_{05}$ of 0.06 µg/kg bw/day for increased skin cancer incidence[37]. The MoEs were below one for all participants of the present study [Table 7]. Mean upper bound exposure for iAs ranged from 0.27 to 0.34 µg/kg bw/day for the total child population in Germany, resulting in MoEs between one and two[24]. The slightly lower values reported in the present study can be attributed to the consideration of the total child population and to differences between data from KiESEL reflecting consumption from 2017 and the VELS study referring to 2002.

Cd

The median Cd exposure for infants and toddlers was 0.32 and 0.30 µg/kg bw/day, respectively. High-consuming infants and toddlers exhibited exposures of 0.48 and 0.64 µg/kg bw/day. Infant formula contributed up to 10% to Cd exposure for mean consumers [Table 5]. European studies showed similar Cd exposure levels. British children (1.5 to 4.5 years) had an average exposure of 0.45 µg/kg bw/day[55], and French infants (7-12 months) and toddlers (1-3 years) had exposures of 0.35 and 0.31 µg/kg bw/day, respectively[40]. EFSA estimated average Cd intake for European infants and toddlers at 0.50 and 0.84 µg/kg bw/day, respectively, slightly higher than the present study's findings. German toddlers had average exposures up to 0.70 and 1.01 µg/kg bw/day at the 95th percentile (upper bound). No data were available for the Cd exposure of German infants[42]. Cd exposure sources varied by age. French infants' Cd exposure from infant foods decreased from 96% (1-4 months) to 18% (1-3 years), while conventional food sources increased from 5% to 82%. Infant formula only contributed substantially to Cd exposure in the first four months of life (72%)[40]. In Europe, infant formula was a significant Cd source for infants and toddlers, accounting for 4% and 3%, respectively. German and Finnish toddlers had higher Cd exposure from infant foods (12%-16%) compared to other European countries (1%-6%) due to higher consumption of infant foods[42]. EFSA established a TWI for Cd in the amount of 2.5 µg/kg bw. Dietary Cd exposure in infants and toddlers reached more than 80% of the TWI, with highly exposed infants reaching up to 178%. Around 30% of infants and toddlers exceeded the TWI [Table 6], similar to French children, where 36% of infants (7-12 months) and 29% of toddlers (1-3 years) exceeded the TWI. Potatoes and potato products, bread, vegetables (excluding potatoes), pasta and mixed dishes contributed most to the Cd exposure of French children in the mentioned age groups[40]. EFSA confirmed that highly exposed children and adolescents could exceed the HBGV[42].

Limitations and uncertainties

When interpreting the results, it should be noted that the study is subject to some limitations and uncertainties. One significant limitation of this study is the exclusion of breastfed children due to a lack of data on breast milk consumption. This exclusion limits the generalizability of the results to all infants. Additionally, the TDS-based exposure assessment considered pooled food samples and the upper tail of the distribution of the concentrations cannot be described. Especially for brand-loyal consumers who prefer certain products, pooling of individual foods can lead to under- or overestimation of exposure. The same applies to individual consumer behavior. Although the TDS approach takes into account the most common preparation methods of a population, systematic preparation and cooking methods or the preferred usage of certain kitchen utensils can lead to higher or lower exposures on an individual basis. Although the results of the BfR MEAL Study allow a comparison of conventional and organic diets, the present study focused on conventionally produced foods. A predominantly organic diet could lead to a different exposure.

The high proportion of measurements below the LOQ for infant formula also leads to uncertainties. The proportion of left-censored data was 50% to 100% for iAs, Cd, Pb, Hg, and Ni. Since the present exposure assessment was based on an upper bound approach, it can be assumed that the real exposure from the consumption of infant formula is lower. Calculations of the contribution of infant formula are based on the powder form of infant formula and, therefore, are not affected by left-censored data for drinking water. In general, the use of drinking water from the MEAL kitchen for exposure assessment does not reflect the variability of substance content as shown for regionally sampled drinking water.

Finally, there are some uncertainties that only affect certain substances. The content of iAs was only assessed for a limited number of foods that were known to contain high levels of iAs. Conversion factors were applied for all other foods to determine the content of iAs from total arsenic. The conversion factors, which considered 70% of total arsenic as iAs, may overestimate the exposure to iAs[31]. The assumption that 100% of Cr content corresponds to Cr(III) and 100% of Hg content of infant formula corresponds to inorganic Hg also leads to uncertainties. The content of Cr(III) and inorganic Hg should be determined directly in food for a reliable exposure assessment for Cr(III) and inorganic Hg.

CONCLUSIONS

The exposure assessment of infants and toddlers to various elements through dietary intake, particularly from infant formula, highlights significant findings and calls for targeted actions to ensure safety and reduce potential risks. The study results, based on data from the BfR MEAL Study, demonstrate varied exposure levels for certain elements. While most elements examined did not exceed the HBGVs, there are notable exceedances of HBGVs, particularly for iAs and Cd.

Food-Based Dietary Guidelines should not only consider the adequate intake of nutrients, but also minimize exposure to harmful elements. For this, monitoring of contaminants of foods consumed by infants and toddlers and subsequent dietary exposure assessments should be continued to provide a reliable basis for future reduction strategies. However, it should be noted that the present exposure assessment is subject to uncertainties. Both exposure from infant formula and total exposure may be overestimated by the applied conservative upper bound approach.

Furthermore, the results of this study indicate a need for further research and provide the basis for comprehensive and specific analyses. Research should particularly focus on the exploration of new data sources and the closure of existing data gaps to ensure reliable exposure estimates. This study highlights a need for occurrence data on Cr(III) and inorganic Hg in infant formula. Regarding consumption data, there is always a need for the most current data to reflect the fast-moving changes in diet for exposure assessment. In this context, it seems sensible to estimate exposure for specific target groups with specific dietary habits (e.g., organic diets). In the future, the results of this study may prompt consideration of multiple exposures through the consumption of infant formula.

DECLARATIONS

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Authors' contributions

Conceptualization, data analysis and interpretation, writing - original draft, writing - review and editing: Höpfner, T.

Conceptualization, literature search, data interpretation, writing - original draft, writing - review and editing: Wollenberg, M.

Conceptualization, data analysis and interpretation, software, writing - original draft: Jäger, A.

Writing - original draft: Stadion, M.

Software, Writing - review and editing: Jung, C.

Review: Klook, A. L.

Conceptualization, supervision, funding acquisition, writing - review and editing: Lindtner, O.

Availability of data and materials

The datasets generated and analyzed during the current study are not yet publicly available. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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